

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Docket No: Q63893

Zvia AGUR, et al.

Appln. No.: 09/827,229

Group Art Unit: 1631

Confirmation No.: 7712

TECH CENTER 1600/2900 Examiner: Marjorie A. MORAN

Filed: April 6, 2001

SYSTEM AND METHODS FOR OPTIMIZED DRUG DELIVERY AND For:

PROGRESSION OF DISEASED AND NORMAL CELLS

INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. §§ 1.97 and 1.98

Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure under 37 C.F.R. § 1.56, Applicant hereby notifies the U.S. Patent and Trademark Office of the documents which are listed on the attached PTO/SB/08 A & B (modified) form and/or listed herein and which the Examiner may deem material to patentability of the claims of the above-identified application.

Copies of the listed references can be found in parent application no. 09/691,053. If that is not the case, please advise and the undersigned attorney will attempt to obtain copies and provide them to the Examiner.

The present Information Disclosure Statement is being filed (without a Statement Under 37 C.F.R § 1.97(e)) after the later of three months from the application's filing date and the mailing date of the first Office Action on the merits, but before a Final Office Action, Notice of

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U.S. Appln. No.: 09/827,229

Allowance, or an action that otherwise closes prosecution in the application (whichever is

earlier), and therefore a check for the fee of \$180.00 under 37 C.F.R. § 1.17(p) is attached. The

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The submission of the listed documents is not intended as an admission that any such

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Respectfully submitted,

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Date: July 8, 2003

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| Substitute for Form 1449 A & B/PTO | Application Number | 09/827,229 |
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| SATEMENT BY APPLICANT | First Named Inventor | Zvia AGUR |
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| | Examiner Name | Marjorie A. MORAN |
| Sheet 1 of 4 | Attorney Docket Number | Q63893 |
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| U.S. PATENT DOCUMENTS | | | | | | | | |
|-----------------------|------------|----|--------------------------------|---|--|--|--|--|
| Examiner Initials* | Kind Code* | | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | | | | |
| | | US | | | | | | |

| | FOREIGN PATENT DOCUMENTS | | | | | | | | |
|---------------------------------------|--------------------------|------------------------------|---------------------|-----------------------------------|------------------|-----------------------------|-------------|--|--|
| Examiner Cite Foreign Patent Document | | | | | Publication Date | Name of Patentee or | 77 | | |
| Initials* | No.1 | Country Code ³ | Number ⁴ | Kind Code ⁵ (if known) | MM-DD-YYYY | Applicant of Cited Document | Translation | | |
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| | | OTHER ART - NON PATENT LITERATURE DOCUMENTS | |
|-----------------------|--------------|--|--------------------------|
| Examiner Initials* | Cite No.1 | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city, and/or country where published. | Translation ⁶ |
| | | R. Stoffel et al., "Thrombopoietin in Thrombocytopenic Mice: Evidence Against Regulation at the mRNA Level and for a Direct Regulatory Role of Platelets," The American Society of Hematology, Blood, vol. 87, | ļ |
| | | no. 2, pp. 567-573, January 15, 1996. | |
| | | Warren S. Alexander, "Thrombopoietin and the c-Mpl receptor: insights from gene targeting," The | |
| - | | International Journal of Biochemistry & Cell Biology, pp. 1027-1035, January 28, 1999. | |
| • | | M. Miyazaki, et al., "The Relationship Between Carboplatin AUC and Serum Thrombopoietin Kinetics in Patients with Lung Cancer," 2 nd Department of Internal Medicine, Hiroshima University School of | |
| | | Medicine, Anti Cancer Research, vol. 19, pp. 667-670 (1999). | |
| | | S. Vadhan-Raj, et al., "Stimulation of Megakaryocyte and Platelet Production by a Single Dose of | |
| | | Recombinant Human Thrombopoietin in Patients with Cancer," Annals of Internal Medicine, vol. 126, no. 9, pp. 673-681, May 1997. | |
| | | HE. Wichmann, et al., "A Mathematical Model of Thrombopoiesis in Rats," Cell Tissue Kinet, vol. 12, pp. 551-567, January 1979. | |
| | | L. A. Harker, et al., "Effects of megakaryocyte growth and development factor on platelet production, | |
| | | platelet life span, and platelet function in healthy human volunteers," The American Society of Hematology, Blood, vol. 95, no. 8, pp. 2514-2522, April 15, 2000. | |
| | | H. Mayani, et al., "Lineage Commitment in Human Hemopoiesis Involves Asymmetric Cell Division of Multipotent Progenitors and Does not Appeal to be Influenced by Cytokines," Journal of Cellular Physiology, vol. 157, pp. 579-586, 1993. | |
| | | David W. Golde, "The Stem Cell," Scientific American, pp. 36-43, December 1991. | |
| | | S. J. Morrison, et al., "The Biology of Hematopoietic Stem Cells," Annu. Rev. Cell Dev. Biol., vol. 11, pp. 35-71, 1995. | |
| | | J. Eller, et al., "Modelling Thrombopoiesis Regulation-I; Model Description and Simulation Results," Comput. Math. Applic., vol. 14, no. 9-12, pp. 841-848, 1987. | |
| | | G. K. von Schulthess, et al., "Oscillating platelet counts in healthy individuals: Experimental investigation | |
| | | and quantitive evaluation of thrombocytopoietic feedback control," Scand J Haematol, vol. 36, pp. 473-479, March 8, 1986. | |
| | | L. A. Harker, et al., "Dose-Response Effects of Pegylated Human Megakaryocyte Growth and Development Factor on Platelet Production and Function in Nonhuman Primates," The American Society of Hematology, Blood, vol. 88, no. 2, pp. 511-521, July 15, 1996. | |

| Examiner Signature | Date Considered |
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Sheet 2 of

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| First Named Inventor | Zvia AGUR |
| Art Unit | 1631 |
| Examiner Name | Marjorie A. MORAN |
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| | | | U.S. I | PATENT DOCUM | MENTS | 22 |
|-----------------------|--------------|-----------------------|-----------------------------------|--------------------------------|---|-----|
| Examiner Initials* | Cite No.1 | Document Nu Number | Mind Code ² (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | - C |
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| FOREIGN PATENT DOCUMENTS | | | | | | | |
|---------------------------------------|------|------------------------------|---------------------|-----------------------------------|------------------|-----------------------------|--------------------------|
| Examiner Cite Foreign Patent Document | | | | | Publication Date | Name of Patentee or | Translation ⁶ |
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| | | OTHER ART - NON PATENT LITERATURE DOCUMENTS | |
|-----------------------|--------------|---|--------------------------|
| Examiner Initials* | Cite No.1 | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city, and/or country where published. | Translation ⁶ |
| | | P. A. Fielder, "Regulation of Thrombopoietin Levels by c-mpl-Mediated Binding to Platelets," The American Society of Hematology, Blood, vol. 87, no. 6, pp. 2154-2161, March 15, 1996. | |
| | | John E. J. Raski, et al., "Molecules in focus; The thrombopoietic factor, Mpl-ligand," The International Journal of Biochemistry & Cell Biology, vol. 30, pp. 657-660, 1998. | ! |
| • | | F. J. de Sauvage, et al., "Physiological Regulation of Early and Late Stages of Megakaryocytopoiesis by Thrombopoietin," Departments of Molecular Biology, Cell Genetics, vol. 183, pp. 651-656, February 1996. | |
| | | F. Tacke, et al., "Endogenous serum levels of thrombopoietic cytokines in healthy whole-blood and platelet donors: implications for plateletpheresis," British Journal of Haematology, vol. 105, pp. 511-513, 1999. | |
| • | | S. A. Burstein, et al., "Megakaryopoiesis and platelet formation," Williams Hematology, 5 th ed., Ch. 118, McGraw-Hill, Inc., 1995. | |
| _ | | R. Schofield, et al., "Self-Maintenance Capacity of CFU-S," Journal of Cellular Physiology, vol. 103, pp. 355-362, 1980. | |
| | | M. Rosendaal, et al., "Organization of Haemopoietic Stem Cells: The Generation-Age Hypothesis," Cell Tissue Kinet., vol. 12, pp. 17-29, 1979. | |
| | | A. Iliadis, et al., "Optimizing Drug Regimens in Cancer Chemotherapy by an Efficacy-Toxicity Mathematical Model," Computers and Biomedical Research, vol. 33, pp. 211-226, 2000. | |
| | | F. L. Pereira, et al., "A new optimization based approach to experimental combination chemotherapy," Frontiers Med. Biol. Engng., vol. 6, no. 4, pp. 257-268, 1995. | |
| | | *Hassin Agur, "Optimizing Chemotherapy Scheduling Using Search Heuristics," pp. 2-36 | |
| - | | Kenji Terashi, et al., "Close Association between Clearance of Recombinant Human Granulocyte Colony-Stimulating Factor (G-CSF) and G-CSF Receptor on Neutrophils in Cancer Patients," Antimicrobial Agents and Chemotherapy, vol. 43, no. 1, pp. 21-24, January 1999. | |
| | | T. H. Price, et al., "Effect of Recombinant Granulocyte Colony-Stimulating Factor on Neutrophil Kenetics in Normal Young and Elderly Humans," The American Society of Hematology, vol. 88, no. 1, pp. 335-340, July 1, 1996. | |
| | | B. I. Lord, et al., "The kinetics of human granulopoiesis following treatment with granulocyte colony-stimulating factor in vivo," Proc. Natl. Acad. Sci. USA, vol. 86, pp. 9499-9503, December 1989. | _ |

| | | |
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| Examiner Signature | Date Considered | |

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| | Examiner Initials* Cite No. 1 Number Kind Code² (if known) | | | | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document |
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| Examiner | Cite | Foreign Patent Document | | | Publication Date | Name of Patentee or | Translation ⁶ |
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| | | OTHER ART - NON PATENT LITERATURE DOCUMENTS | |
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| | | J. Y. Mary, "Normal Human Granulopoiesis Revisited. I. Blood Data," Biomedicine & Pharmacotherapy, vol. 38, pp. 33-43, 1984. | |
| | - | J. Y. Mary, "Normal Human Granulopoiesis Revisited. II. Bone Marrow Data," Biomedicine & Pharmacotherapy, vol. 38, pp. 66-77, 1984. | |
| | | C. Dresch, et al., "Growth fraction of myelocytes in normal human granulopoiesis," Cell Tissue Kinet. vol. 19, pp. 11-22, 1986. | |
| | | S. Schmitz, et al., "The effect of continuous G-CSF application in human cyclic neutropenia: a model analysis," British Journal of Haematology, vol. 90, pp. 41-47, 1995. | |
| | | S. Schmitz, et al., "Quantification of the cell kinetic effects of G-CSF using a model of human granulopoiesis," International Society for Experimental Hematology, Experimental Hematology, vol. 21, pp. 755-760, 1993. | |
| | | L. A. Harker, et al., "Regulation of Platelet Production and Function by Megakaryocyte Growth and Development Factor in Nonhuman Primates," The American Society of Hematology, no. 5, pp. 1833-1844, March 1996. | |
| | | Warren S. Alexander, "Thrombopoietin," The Walter and Eliza Hall Inst. for Medical Research, Growth Factors, vol. 17, pp. 13-24, 1999. | |
| | | Kenneth Kaushansky, "Thrombopoietin: The Primary Regulator of Platelet Production," The Journal of The American Society of Hematology, Blood, vol. 86, no. 2, pp. 419-431, July 15, 1995. | |
| | | Saroj Vadhan-Raj, "Recombinant Human Thrombopoietin: Clinical Experience and In Vivo Biology," Seminars in Hematology, vol. 35, No. 3, pp. 261-268, July 1998. | |
| ' '' | | Laurence A. Harker, "Physiology and clinical applications of platelet growth factors," Curr Opin Hematol, vol. 6, pp. 127-134, 1999. | |
| | | Jack Levin, "Thrombopoietin Clinically Realized?," The New England Journal of Medicine, vol. 336, no. 6, pp. 1-3, February 6, 1997. | |
| | | G. Somlo, et al., "Recombinant Human Thrombopoietin in Combination with Granulocyte Colony-Stimulating Factor High-Dose Chemotherapy," The American Society of Hematology, Blood, vol. 93, no. 9, pp. 2798-2806, May 1, 1999. | |
| | | K. J. Neelis, et al., "The Efficacy of Single-Dose Administration of Thrombopoietin with Coadministration Myelosuppressed Rhesus Monkeys," The American Society of Hematology, Blood, vol. 90, no. 7, pp. 2565-2573, October 1, 1997. | |

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| Initials* No.¹ journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city, and/or country where published. L. J. Murray, et al., "Thrombopoietin Mobilizes Cd34+ Cell Subsets Into Peripheral Blood And Expands Multilineage Progenitors In Bone Marrow Of Cancer Patients With Normal Hematopoiesis," Experimental Hematology, vol. 26, pp. 207-216, 1998. R. L. Basser, et al., "Randomized, Blinded, Placebo-Controlled Phase I Trial of Pegylated Recombinant Human Megakaryocyte Growth and Development Factor with Filgrastim after Dose-Intensive Chemotherapy in Patients with Advanced Cancer," The American Society of Hematology, Blood, Vol. 89, no. 9, pp. 3118-3128, 1997. D. Zucker-Franklin, "The Ultrastructure of Megakaryocytes and Platelets," Dept. of Medicine and Rheumatic Diseases Study Group, New York, The Platelets, Ch. 55, pp. 1553-1629. L. A. Harker, et al., "Thrombokinetics in Man," The Journal of Clinical Investigation, vol. 48, pp. 963-974, 1969. Laurence H. Harker, "Thrombokinetics in Idiopathic Thrombocytopenic Purpura," British Journal of Haematology, pp. 95-104, 1970. R. Sungaran, et al., "Localization and Regulation of Thrombopoietin mRNA Expression in Human Kidney, Liver, Bone Marrow, and Spleen Using in Situ Hybridization," The American Society of Hematology, Blood, vol. 89, no. 1, pp. 101-107, 1997. Y. Nagata, et al., "Serum Thrombopoietin Level is not Regulated by Transcription but by the Total Counts of both Megakaryocytes and Platelets during Thrombocytopenia and Thrombocytosis," Tsukuba Life Science Center, Thrombosis and Haemostasis, vol. 77, pp. 808-814, 1997. H. Nagahisa, et al., "Bone Marrow Stromal Cells Produce Thrombopoietin and Stimulate Magakaryocyte Growth and Maturation but Suppress Proplatelet Formation," The American Society of Hematology, Blood, vol. 87, no. 4, pp. 1309-1316, February 15, 1996. 1. Athanassios, et al., "Comparison Between Optimata's Claims and Contemporary, 'state of the art' in Optimizing of Anticancer Chemotherapy," Computer | **** | OTHER ART - NON PATENT LITERATURE DOCUMENTS | |
|--|------|--|--------------------------|
| Multilineage Progenitors In Bone Marrow Of Cancer Patients With Normal Hematopoiesis," Experimental Hematology, vol. 26, pp. 207-216, 1998. R. L. Basser, et al., "Randomized, Blinded, Placebo-Controlled Phase I Trial of Pegylated Recombinant Human Megakaryocyte Growth and Development Factor with Filgrastim after Dose-Intensive Chemotherapy in Patients with Advanced Cancer," The American Society of Hematology, Blood, Vol. 89, no. 9, pp. 3118-3128, 1997. D. Zucker-Franklin, "The Ultrastructure of Megakaryocytes and Platelets," Dept. of Medicine and Rheumatic Diseases Study Group, New York, The Platelets, Ch. 55, pp. 1553-1629. L. A. Harker, et al., "Thrombokinetics in Man," The Journal of Clinical Investigation, vol. 48, pp. 963-974, 1969. Laurence H. Harker, "Thrombokinetics in Idiopathic Thrombocytopenic Purpura," British Journal of Haematology, pp. 95-104, 1970. R. Sungaran, et al., "Localization and Regulation of Thrombopoietin mRNA Expression in Human Kidney, Liver, Bone Marrow, and Spleen Using in Situ Hybridization," The American Society of Hematology, Blood, vol. 89, no. 1, pp. 101-107, 1997. Y. Nagata, et al., "Serum Thrombopoietin Level is not Regulated by Transcription but by the Total Counts of both Megakaryocytes and Platelets during Thrombocytopenia and Thrombocytosis," Tsukuba Life Science Center, Thrombosis and Haemostasis, vol. 77, pp. 808-814, 1997. H. Nagahisa, et al., "Bone Marrow Stromal Cells Produce Thrombopoietin and Stimulate Magakaryocyte Growth and Maturation but Suppress Proplatelet Formation," The American Society of Hematology, Blood, vol. 87, no. 4, pp. 1309-1316, February 15, 1996. 1. Athanassios, et al., "Comparison Between Optimata's Claims and Contemporary, 'state of the art' in Optimizing of Anticancer Chemotherapy," Computers and Biomedical Research, vol. 33, pp. 211-226, 2000. Hui-Chi Hsu, et al., "Circulating Levels of Thrombopoietic and Inflammatory Cytokines in Patients with | | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city, and/or country where published. | Translation ⁶ |
| Human Megakaryocyte Growth and Development Factor with Filgrastim after Dose-Intensive Chemotherapy in Patients with Advanced Cancer," The American Society of Hematology, Blood, Vol. 89, no. 9, pp. 3118-3128, 1997. D. Zucker-Franklin, "The Ultrastructure of Megakaryocytes and Platelets," Dept. of Medicine and Rheumatic Diseases Study Group, New York, The Platelets, Ch. 55, pp. 1553-1629. L. A. Harker, et al., "Thrombokinetics in Man," The Journal of Clinical Investigation, vol. 48, pp. 963-974, 1969. Laurence H. Harker, "Thrombokinetics in Idiopathic Thrombocytopenic Purpura," British Journal of Haematology, pp. 95-104, 1970. R. Sungaran, et al., "Localization and Regulation of Thrombopoietin mRNA Expression in Human Kidney, Liver, Bone Marrow, and Spleen Using in Situ Hybridization," The American Society of Hematology, Blood, vol. 89, no. 1, pp. 101-107, 1997. Y. Nagata, et al., "Serum Thrombopoietin Level is not Regulated by Transcription but by the Total Counts of both Megakaryocytes and Platelets during Thrombocytopenia and Thrombocytosis," Tsukuba Life Science Center, Thrombosis and Haemostasis, vol. 77, pp. 808-814, 1997. H. Nagahisa, et al., "Bone Marrow Stromal Cells Produce Thrombopoietin and Stimulate Magakaryocyte Growth and Maturation but Suppress Proplatelet Formation," The American Society of Hematology, Blood, vol. 87, no. 4, pp. 1309-1316, February 15, 1996. I. Athanassios, et al., "Comparison Between Optimata's Claims and Contemporary, 'state of the art' in Optimizing of Anticancer Chemotherapy," Computers and Biomedical Research, vol. 33, pp. 211-226, 2000. Hui-Chi Hsu, et al., "Circulating Levels of Thrombopoietic and Inflammatory Cytokines in Patients with | - | Multilineage Progenitors In Bone Marrow Of Cancer Patients With Normal Hematopoiesis," Experimental Hematology, vol. 26, pp. 207-216, 1998. | |
| D. Zucker-Franklin, "The Ultrastructure of Megakaryocytes and Platelets," Dept. of Medicine and Rheumatic Diseases Study Group, New York, The Platelets, Ch. 55, pp. 1553-1629. L. A. Harker, et al., "Thrombokinetics in Man," The Journal of Clinical Investigation, vol. 48, pp. 963-974, 1969. Laurence H. Harker, "Thrombokinetics in Idiopathic Thrombocytopenic Purpura," British Journal of Haematology, pp. 95-104, 1970. R. Sungaran, et al., "Localization and Regulation of Thrombopoietin mRNA Expression in Human Kidney, Liver, Bone Marrow, and Spleen Using in Situ Hybridization," The American Society of Hematology, Blood, vol. 89, no. 1, pp. 101-107, 1997. Y. Nagata, et al., "Serum Thrombopoietin Level is not Regulated by Transcription but by the Total Counts of both Megakaryocytes and Platelets during Thrombocytopenia and Thrombocytosis," Tsukuba Life Science Center, Thrombosis and Haemostasis, vol. 77, pp. 808-814, 1997. H. Nagahisa, et al., "Bone Marrow Stromal Cells Produce Thrombopoietin and Stimulate Magakaryocyte Growth and Maturation but Suppress Proplatelet Formation," The American Society of Hematology, Blood, vol. 87, no. 4, pp. 1309-1316, February 15, 1996. I. Athanassios, et al., "Comparison Between Optimata's Claims and Contemporary, 'state of the art' in Optimizing of Anticancer Chemotherapy," Computers and Biomedical Research, vol. 33, pp. 211-226, 2000. Hui-Chi Hsu, et al., "Circulating Levels of Thrombopoietic and Inflammatory Cytokines in Patients with | | Human Megakaryocyte Growth and Development Factor with Filgrastim after Dose-Intensive Chemotherapy in Patients with Advanced Cancer," The American Society of Hematology, Blood, Vol. 89, | |
| L. A. Harker, et al., "Thrombokinetics in Man," The Journal of Clinical Investigation, vol. 48, pp. 963-974, 1969. Laurence H. Harker, "Thrombokinetics in Idiopathic Thrombocytopenic Purpura," British Journal of Haematology, pp. 95-104, 1970. R. Sungaran, et al., "Localization and Regulation of Thrombopoietin mRNA Expression in Human Kidney, Liver, Bone Marrow, and Spleen Using in Situ Hybridization," The American Society of Hematology, Blood, vol. 89, no. 1, pp. 101-107, 1997. Y. Nagata, et al., "Serum Thrombopoietin Level is not Regulated by Transcription but by the Total Counts of both Megakaryocytes and Platelets during Thrombocytopenia and Thrombocytosis," Tsukuba Life Science Center, Thrombosis and Haemostasis, vol. 77, pp. 808-814, 1997. H. Nagahisa, et al., "Bone Marrow Stromal Cells Produce Thrombopoietin and Stimulate Magakaryocyte Growth and Maturation but Suppress Proplatelet Formation," The American Society of Hematology, Blood, vol. 87, no. 4, pp. 1309-1316, February 15, 1996. I. Athanassios, et al., "Comparison Between Optimata's Claims and Contemporary, 'state of the art' in Optimizing of Anticancer Chemotherapy," Computers and Biomedical Research, vol. 33, pp. 211-226, 2000. Hui-Chi Hsu, et al., "Circulating Levels of Thrombopoietic and Inflammatory Cytokines in Patients with | | D. Zucker-Franklin, "The Ultrastructure of Megakaryocytes and Platelets," Dept. of Medicine and | |
| Haematology, pp. 95-104, 1970. R. Sungaran, et al., "Localization and Regulation of Thrombopoietin mRNA Expression in Human Kidney, Liver, Bone Marrow, and Spleen Using in Situ Hybridization," The American Society of Hematology, Blood, vol. 89, no. 1, pp. 101-107, 1997. Y. Nagata, et al., "Serum Thrombopoietin Level is not Regulated by Transcription but by the Total Counts of both Megakaryocytes and Platelets during Thrombocytopenia and Thrombocytosis," Tsukuba Life Science Center, Thrombosis and Haemostasis, vol. 77, pp. 808-814, 1997. H. Nagahisa, et al., "Bone Marrow Stromal Cells Produce Thrombopoietin and Stimulate Magakaryocyte Growth and Maturation but Suppress Proplatelet Formation," The American Society of Hematology, Blood, vol. 87, no. 4, pp. 1309-1316, February 15, 1996. I. Athanassios, et al., "Comparison Between Optimata's Claims and Contemporary, 'state of the art' in Optimizing of Anticancer Chemotherapy," Computers and Biomedical Research, vol. 33, pp. 211-226, 2000. Hui-Chi Hsu, et al., "Circulating Levels of Thrombopoietic and Inflammatory Cytokines in Patients with | | L. A. Harker, et al., "Thrombokinetics in Man," The Journal of Clinical Investigation, vol. 48, pp. 963-974, | |
| R. Sungaran, et al., "Localization and Regulation of Thrombopoietin mRNA Expression in Human Kidney, Liver, Bone Marrow, and Spleen Using in Situ Hybridization," The American Society of Hematology, Blood, vol. 89, no. 1, pp. 101-107, 1997. Y. Nagata, et al., "Serum Thrombopoietin Level is not Regulated by Transcription but by the Total Counts of both Megakaryocytes and Platelets during Thrombocytopenia and Thrombocytosis," Tsukuba Life Science Center, Thrombosis and Haemostasis, vol. 77, pp. 808-814, 1997. H. Nagahisa, et al., "Bone Marrow Stromal Cells Produce Thrombopoietin and Stimulate Magakaryocyte Growth and Maturation but Suppress Proplatelet Formation," The American Society of Hematology, Blood, vol. 87, no. 4, pp. 1309-1316, February 15, 1996. I. Athanassios, et al., "Comparison Between Optimata's Claims and Contemporary, 'state of the art' in Optimizing of Anticancer Chemotherapy," Computers and Biomedical Research, vol. 33, pp. 211-226, 2000. Hui-Chi Hsu, et al., "Circulating Levels of Thrombopoietic and Inflammatory Cytokines in Patients with | | | |
| of both Megakaryocytes and Platelets during Thrombocytopenia and Thrombocytosis," Tsukuba Life Science Center, Thrombosis and Haemostasis, vol. 77, pp. 808-814, 1997. H. Nagahisa, et al., "Bone Marrow Stromal Cells Produce Thrombopoietin and Stimulate Magakaryocyte Growth and Maturation but Suppress Proplatelet Formation," The American Society of Hematology, Blood, vol. 87, no. 4, pp. 1309-1316, February 15, 1996. I. Athanassios, et al., "Comparison Between Optimata's Claims and Contemporary, 'state of the art' in Optimizing of Anticancer Chemotherapy," Computers and Biomedical Research, vol. 33, pp. 211-226, 2000. Hui-Chi Hsu, et al., "Circulating Levels of Thrombopoietic and Inflammatory Cytokines in Patients with | | R. Sungaran, et al., "Localization and Regulation of Thrombopoietin mRNA Expression in Human Kidney, Liver, Bone Marrow, and Spleen Using in Situ Hybridization," The American Society of Hematology, | |
| H. Nagahisa, et al., "Bone Marrow Stromal Cells Produce Thrombopoietin and Stimulate Magakaryocyte Growth and Maturation but Suppress Proplatelet Formation," The American Society of Hematology, Blood, vol. 87, no. 4, pp. 1309-1316, February 15, 1996. I. Athanassios, et al., "Comparison Between Optimata's Claims and Contemporary, 'state of the art' in Optimizing of Anticancer Chemotherapy," Computers and Biomedical Research, vol. 33, pp. 211-226, 2000. Hui-Chi Hsu, et al., "Circulating Levels of Thrombopoietic and Inflammatory Cytokines in Patients with | | of both Megakaryocytes and Platelets during Thrombocytopenia and Thrombocytosis," Tsukuba Life | |
| Optimizing of Anticancer Chemotherapy," Computers and Biomedical Research, vol. 33, pp. 211-226, 2000. Hui-Chi Hsu, et al., "Circulating Levels of Thrombopoietic and Inflammatory Cytokines in Patients with | | H. Nagahisa, et al., "Bone Marrow Stromal Cells Produce Thrombopoietin and Stimulate Magakaryocyte Growth and Maturation but Suppress Proplatelet Formation," The American Society of Hematology, Blood, | |
| | | I. Athanassios, et al., "Comparison Between Optimata's Claims and Contemporary, 'state of the art' in Optimizing of Anticancer Chemotherapy," Computers and Biomedical Research, vol. 33, pp. 211-226, 2000. | |
| Ciona and reactive filluminocytosis, J Lab Cin Med, vol. 154, no. 4, pp. 572-571, 1777. | | Hui-Chi Hsu, et al., "Circulating Levels of Thrombopoietic and Inflammatory Cytokines in Patients with Clonal and Reactive Thrombocytosis," J Lab Clin Med, vol. 134, no. 4, pp. 392-397, 1999. | |

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